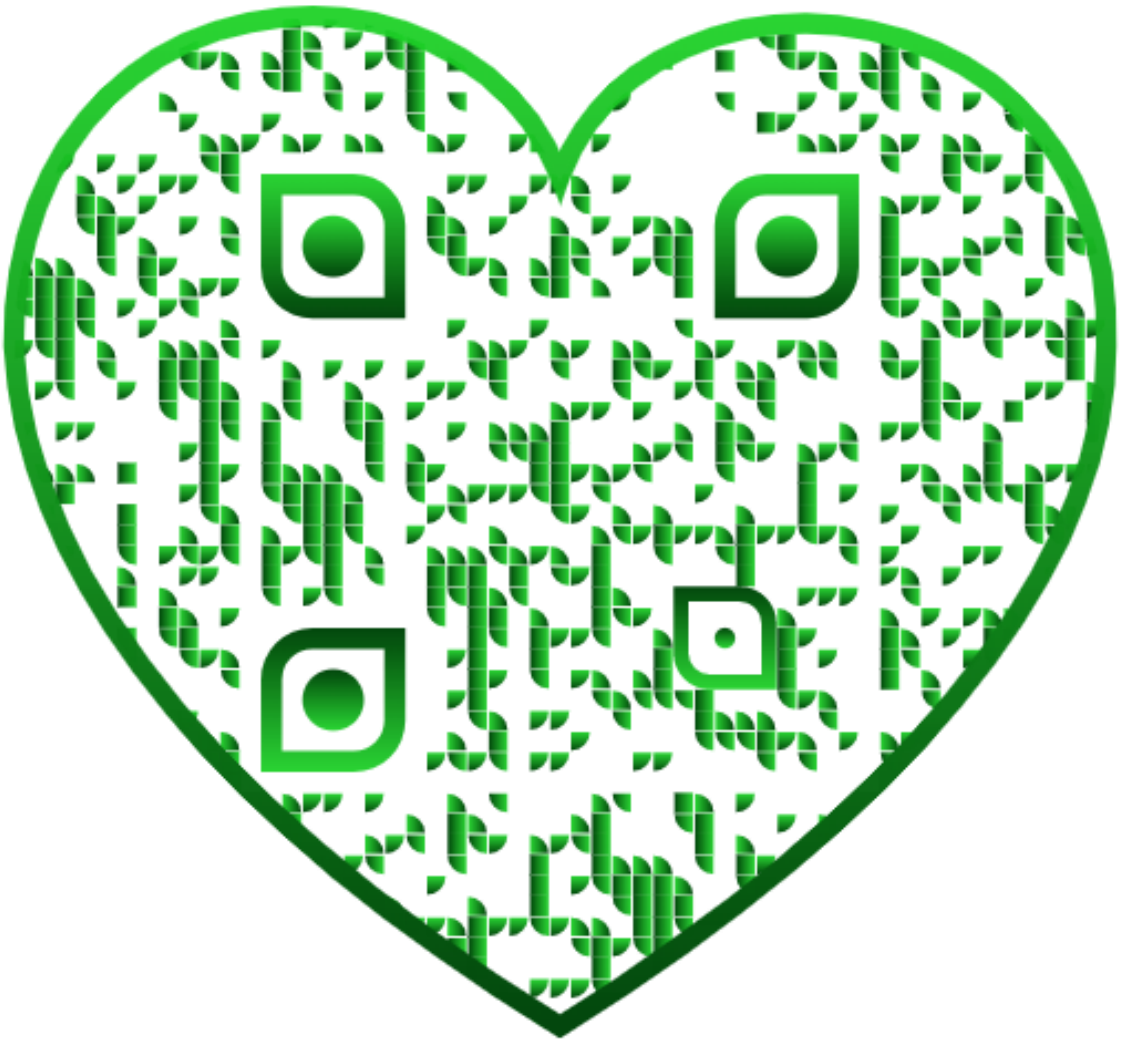
10. Veterinary Pharmaceutical Dosage Forms



Introduction

- VDF are dosage forms used to treat, prevent, and/or control animal disease.
- They should be able to treat and prevent animal disease and suffering.
- Just like humans the animals receive medicines to keep them healthy.

- The development of pharmaceuticals for humans and animals are generally the same.

- Animals can be conveniently grouped into:
  - Food producing animals
  - Companion animals (like cats, dogs and horses)
  - Exotic animals (like Birds and Rabbits)

- The market for animal health products can be grouped into three major categories:
  - Pharmaceuticals (Medicines)
  - Neutraceuticals (Animal feed)
  - Biologicals (Vaccines)
- Any animal product should exhibit acceptable **safety**, **efficacy**, and **stability** profiles.

- The major **challenges** in designing and developing VDFs include:
  - **Interspecies and intraspecies differences**
    - A wide variety in both anatomy and physiology within and between species, which in turn result in differences in ADME.
    - Differ in size, habit, and social behavior.
  - **Formulation**
  - **Economics**

- Development of veterinary products is more difficult:
  - A smaller overall commercial market
  - A smaller profit margin
  - A shorter time line to drug approval
  - A greater variety of animal species
    - A greater variety of physiological differences
  - Dose is calculated based on animal weight

- Some unique features in animals:
  - Diversity of species and breeds
  - Range of body sizes
  - Regional differences
  - Differences in metabolism
  - Differences in disease state
  - Differences in feeding habits

Selection and Classification basis for VDFs

- Each species of animals has certain distinguishing features.
- Some of these features contribute to variation in handling of drugs
- The animal kingdom can be classified based on:
  - Dietary habits
  - Physiological basis

Dietary habits

- Provide the most satisfactory basis for grouping of animals.
- Based on their feeding habits animals are classified as:
  - Herbivores
  - Carnivores
  - Omnivores

Physiological basis

- Digestive system provide a distinguishing feature among animals, specially between herbivores and carnivores
- Hepatic microsomal enzymes
- Urinary pH
  - Herbivore – Alkaline pH
  - Carnivore – Acidic pH
  - Omnivores – Wider range of pH

- Variations in anatomical/physiological components between animal species:
  - **Digestive system**
    - Anatomical arrangements of the **GIT** and **Dietary** habits are the very important features that distinguish animal species
    - Based on their digestive system, two categories of animals:

1. **Monogastric** – single stomach species (e.g. pig, dog, and cat)
2. **Polygastric** – more than one stomach (ruminants)

- Species variations in the capacities of the digestive system:

Components	Relative capacities (%)		
	Horse	Pig	Dog
Stomach	8.5	29.2	62.3
Small intestine	30.2	33.5	23.3
Cecum	15.9	5.6	1.3
Large colon	38.4	31.7	13.1
Rectum	7.0		

- **Skin**
  - The most accessible and largest organ.
  - The proportions of the skin components vary from species to species.
    - Horses ~ highly developed sweat gland
    - Cats and dogs ~ don’t sweat properly
    - Sheep and goats ~ secret more sebum
    - Pigs ~ an extensive layer of keratin

- **Liver and Kidney**
  - These are the principal metabolizing and eliminating organs for drugs.
  - Liver to Kidney ratio is greater in humans.
  - **Metabolism**
    - Herbivores have highly developed hepatic microsomal system
    - Dogs don't have acetylation
    - Cats have poorly developed glucosamine conjugation

- **Renal excretion**

  - The GFR differs from species to species

	GFR (ml/min/Kg)
Horses	1.63
Cattles	1.8 – 2.4
Dogs and Cats	3.5 – 4.0

- Human and veterinary dosage forms

Similarities

- Basic principles of pharmaceutics
  - Preformulation
  - Physicochemical principles
  - Packaging
  - Stability issues
  - Compatibility
  - Sterility …

Differences

- Specificity
  - Veterinary dosage forms are more specific for a single species
- Route of administration
  - Some specific routes are suitable for animals
    - Intramammary
    - Lavage
    - Intraperitonial
    - With drinking water or feeding

Routes of administration and Dosage forms

Oral dosage forms

- Solutions, Emulsions, and Suspensions ~ administered by nasogastric tube, oral syringes or with feeds.
- Pastes and gels ~ preloaded calibrated syringe is used.
- Capsules, Tablets, Powders and Granules
- Blocks (Feed/Water/Lick)

Parenteral dosage forms

- Include
  - Aqueous or oily solutions, Emulsions or Suspensions
  - Solid forms for implantation.
- Routes ~ IV, IM, and SC
- IV injectables should be ~ Sterile, Isotonic, and Pyrogen free.
- Principle of administration are similar to that of humans.

Topical dosage forms

- Widely used dosage forms - less labor is required.
- Can be used both for local and systemic effects.
- Selection of vehicle is very important, as this determines the absorption.
- E.g. Dusting powders, Liniments, Lotions, Creams and Ointments, Aerosols, Pour on formulations, and Transdermal patches.

Preparations for body cavities

- **Rectal** – glucose, digested proteins
- **Vaginal** – vaginal tablets, reproductive hormones
- **Otic** - Solutions, Suspensions, Ointments, Powders, Otic cones
- **Intranasal** – inhaled drugs (sprays and mist dispersions may be used)
- **Ophthalmic** - Sterile aqueous or oily solutions, suspensions emulsions or ointments meant for application by instillation.

- **Implants** - two types
  - **Implantable infusion devices** - Implanted percutaneously
    - E.g. Vapor pressure powered device, and Programmable implants
  - **Sub-dermal implants**

Administration devices and technologies

Drinking water metering devices

- Medication of large number of animals can be accomplished.
- Regulated amount of a soluble drug is added to drinking water.
    - E.g. Antibiotics, Vaccines, Anthelmentics

Feed

- E.g. Blocks, Pellets, Liquids

Movement

- This relies on the natural and voluntary movement of healthy animals to dispense medications.
    - Dust bags – for topical application of powders
    - Cattle ear tags – flexible plastic ear tags are used
    - Cattle Hog rubs – rope staked in insecticide solutions
    - Automatic oilers – rope saturated with oily insecticide
    - Flea and Tick Collars – for dogs and Cats

Oral Devices

- Balling guns
- Esophageal delivery devices – syringes and tubes
- Drenchers – to give an animal a large dose of medicine in a liquid by mouth
- Paste dosers – Syringes, Caulking guns (prefilled cartridges)
- Powder guns

Topical applicators

- Sprayers
- Dip bath
- Pour on and spot on applications
- Ointment and paste applicators
- Aerosol dispensers

Parenterals

- Injection needles
- Syringes – single use, single dose, multiple dose
- injector pole – for injecting dangerous animals

Dosage form design

Solids

- The primary solid dosage forms for veterinary medicine including tablets, capsules, and feed additives.
- ***Tablets***
  - Tablets are used in a wide variety of indications, with several species.
  - Are available in a large size range, and are manufactured by several different processes.

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- The primary species treated with tablets are dogs and cats.
- However, for some indications, cattle and sheep may receive a large tablet (often referred to as a bolus)
- In general, the manufacturing processes used for the majority of these tablets are the same as those used for humans

- Tablets can be coated:
  - To differentiate the product by color,
  - To help mitigate offensive-tasting compounds, or
  - To prevent dusting in the bottle
- The relative size of the tablets for companion animals are somewhat similar to those used for humans.

- The tablet sizes for cattle, sheep, and horses are larger to incorporate the larger amount of active ingredient and facilitate administration.
    - These tablets are typically called **boluses** and are often oblong for easier administration
- Tablets are mainly formulated as immediate release types with once to twice-daily dosing for the course of therapy depending on the disease being treated.
- Because of the faster GIT motility in dogs and cats, it is fairly difficult to achieve once-daily dosing.

- ***Capsules***

  - Like tablets, capsules are mainly used for dogs and cats, but there are some vitamin and mineral supplement capsules formulated for cattle.

  - While the typical gelatin capsules used for humans can be used for veterinary medicine if the doses are small (e.g. Sizes No 000, No 00), there are very large veterinary capsules that range in sizes from No 13 (2 - 3 g) to No 7 (14 - 24 g).

Empty Hard Gelatin Capsule Physical Specifications			
Size	**Outer Diameter (mm)**	**Height or Locked Length (mm)**	**Actual Volume (ml)**
Su07	23.4	88.5	28
7	23.4	78.0	24
10	23.4	64.0	18
11	20.9	47.5	10
12el	15.5	57.0	7.5
12	15.3	40.5	5
13	15.3	30.0	3.2
000	9.97	26.14	1.37
00	8.53	23.30	0.95
0	7.65	21.7	0.68
1	6.91	19.4	0.50
2	6.35	18.0	0.37
3	5.82	15.9	0.30
4	5.31	14.3	0.21
5	4.91	11.1	0.13
Size	**Outer Diameter (mm)**	**Height or Locked Length (mm)**	**Actual Volume (ml)**

- There are fewer capsule animal health products on the market when compared with the human health care market.
  - Despite capsules are often thought to take less time to develop
  - One possible reason for there not being more animal health capsule formulation is that the **eating action** of cats and dogs would result in capsules being split and spill the contents.
  - If the drug contained in the capsule is associated with a bad taste, then the cat (dog) will be more careful to accept that product on a subsequent occasion.

- ***Feed Additives***

  - Feed additives are useful dosage forms for treating large numbers of animals simultaneously.

  - Dosage forms include solid powders, which are mixed with feeds and liquids that are mixed in the feeds.

  - Products that can be placed into the drinking systems could also be classified as feed additives.

  - Challenges with developing feed additives reside in blend homogeneity and stability

- ***Liquids***
  - Administered via the mouth, injected, or placed on the skin.
  - Oral liquids, parenteral liquids, and dermal/transdermal liquids
- ***Long acting formulations***
  - Reduction of stress to animals
  - Reduce herding
  - Reduce labor cost

- ***Intra-ruminal Bolus formulations***
  - These are products administered to and retained in the rumen of ruminant animals.
  - Formulated to deliver drugs over extended periods.
- ***Intravaginal formulations (Devices)***
  - Hormones to control the estrous cycle
  - E.g. Progestrone releasing intravaginal device, and Sponge delivery systems (Polyurethane impreginated with a potent progestagen)

- ***Collars and Spot-ons***
  - The collar is worn by the animal and the API is slowly delivered.
  - Can be either matrix, reservoir, or mechanical device.